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| 10/650,057 | 08/26/2003 | Magnus Von Knebel Doeberitz | 05033.0002.CPUS02 | 7373 |
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| HOWREY LLP C/O IP DOCKETING DEPARTMENT 2941 FAIRVIEW PARK DRIVE, SUITE 200 FALLS CHURCH, VA 22042-2924 | | | | RAWLINGS, STEPHEN L |
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DATE MAILED: 08/16/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| | | |
|------------------------------|----------------------------------------|-----------------------------|
| Office Action Summary | Application No. | Applicant(s) |
| | 10/650,057 | VON KNEBEL DOEBERITZ ET AL. |
| | Examiner Stephen L. Rawlings, Ph.D. | Art Unit 1643 |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 06 May 2006.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-18 is/are pending in the application.
- 4a) Of the above claim(s) 7-18 is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 1-6 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on 26 March 2003 is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date <u>20040108;20060615</u> | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| | 6) <input checked="" type="checkbox"/> Other: <u>IDS:20060628</u> |

DETAILED ACTION

1. The election filed May 5, 2006, is acknowledged and has been entered.

Applicant has elected the invention of Group I, claims 1-6, drawn to a method of detecting cervical carcinomas, cervical intraepithelial neoplasias or cervical carcinomas.

Because Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 1-18 are pending in the application. Claims 7-18 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

3. Claims 1-6 are currently under prosecution.

Information Disclosure Statement

4. The information disclosures filed January 8, 2004, June 15, 2006, and June 28, 2006, have been considered. An initialed copy of each is enclosed.

Priority

5. Acknowledgment is made of Applicant's claim for foreign priority based on an application filed at the European Patent Office on August 1, 2002. It is noted, however, that applicant has not filed a certified copy of European Patent Office Application No. 02017313.4, as required by 35 U.S.C. 119(b). Accordingly, Applicant has not complied with the requirement set forth Applicant is reminded that in order for a patent issuing on the instant application to obtain the benefit of priority based on priority papers filed in parent Application No. 10/633,484 under 35 U.S.C. 119(a)-(d) or (f), a claim for such foreign priority must be timely made in this application. To satisfy the requirement of 37 CFR 1.55(a)(2) for a certified copy of the foreign application, applicant may simply identify the application containing the certified copy.

6. Applicant's claim under 35 USC § 120 for benefit of the earlier filing date of U.S. Patent Application No. 09/743,103, filed August 3, 2001, which claims benefit of PCT Application No. PCT/DE99/02094, filed July 1, 1999, which claims benefit of German Patent Application No. 198 29 473.5, filed July 1, 1998, is acknowledged.

In addition, Applicant's claims under 35 USC § 120 for benefit of the earlier filing date of U.S. Patent Application No. 10/633,484, filed July 31, 2003, which claims benefit of European Patent Office Application No. 02017313.4, filed August 1, 2002, is acknowledged.

However, claims 1-6 do not properly benefit under 35 U.S.C. § 120 by the earlier filing dates of the priority documents claimed, since the specification of earlier filed U.S. Patent Application No. 09/743,103 does not describe the claimed method, which comprising the step of *solubilizing the cervical body sample in a lysis buffer* before determining the overexpression of cyclin dependent kinase inhibitor p16.

Furthermore, claim 4 does not properly benefit under 35 U.S.C. § 120 by the earlier filing dates of the priority documents claimed, since the specification of earlier filed U.S. Patent Application No. 10/633,484 does not describe the method according to claim 4, wherein the determination of the level of cyclin dependent kinase inhibitor p16 in a healthy human cervical sample is *carried out once for each lot of detection reagents*.

To receive benefit of the earlier filing date under 35 USC §§ 119 and/or 120, the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

Accordingly, the effective filing date of present claims 1-3, 5, and 6 is deemed the filing date of U.S. Patent Application No. 10/633,484, namely July 31, 2003; whereas

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the effective filing date of claim 4 is the filing date of the instant application (i.e., August 26, 2003).

Grounds of Objection

Specification

7. The specification is objected to for the following reason:

At page 1, paragraph 1, of the specification there is a statement that this application is a continuation-in-part of Application Serial No. 09/743,103. The prior filed application has since issued as U.S. Patent No. 6,709,832; yet the specification does not properly indicate the status of this application. Appropriate correction is required.

8. The specification is objected to because the brief description of Figure 1 at page 3 describes Figure 2, whereas the brief description of Figure 2 describes Figure 1. Appropriate correction is required.

9. The specification is objected to because the use of improperly demarcated trademarks has been noted in this application. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

An example of such an improperly demarcated trademark appearing in the specification is Tween™, which is found, for example, at in paragraph [0030] of the published application¹.

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine

¹ U.S. Patent Application Publication No. 2004/0180388 A1.

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under "USPTO Search Collections" on the Internet at
<http://www.uspto.gov/web/menu/search.html>.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

11. Claims 1 and 3-6 rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,709,832 B1, as evidenced by Geraerts et al. (*Am. J. Pathol.* 1999 Jun; **154** (6): 1665-1671).

U.S. Patent No. 6,709,832 B1 (Von Knebel Doeberitz et al.) teaches a method for detecting cervical carcinomas, cervical intraepithelial neoplasias, or cervical carcinomas *in situ*; see entire document (e.g., the Abstract; the disclosure at column 2, lines 15-22; the Examples at columns 3-5; claim 1). According to the disclosure, the process comprises determining the overexpression of cyclin-dependent kinase inhibitor p16 in a human cervical body sample by comparing the expression level of cyclin-dependent kinase inhibitor p16 within said sample to the expression level present in a healthy human cervical body sample; see, e.g., column 4, Table 1; claim 1). The human cervical body sample is selected from a blood sample, a smear, a sputum sample, urine, bone marrow, an organ punctuate or aspirate, a biopsy, a preserved cytological or histological specimen, and a fixed cell or tissue preparation; see, e.g., column 2, lines 33-40; column 3, line 35, through column 4, line 66. The determination of the overexpression is made by any of various methods, including in particular Western blot, ELISA, and immunoprecipitation; see, e.g., column 2, lines 51-56. Von Knebel Doeberitz et al. teaches the expression level present in a healthy human cervical body

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sample is determined from a standardized sample; see, e.g., column 2, lines 45-50. Otherwise, Von Knebel Doeberitz et al. teaches the expression level present in a healthy human cervical body sample is determined using a representative number of healthy human cervical samples during the course of the detection procedure, as exemplified by Example 1 at columns 3 and 4.

Notably, Von Knebel Doeberitz et al. does not expressly teach the process by which the overexpression of p16 is determined comprises lysing the cells and solubilizing the protein. Nonetheless, Von Knebel Doeberitz et al. teaches the determination is made by Western blot analysis, a process briefly described by Example 2 at column 4, lines 55-67, which involves the preparation of cell extracts; and as evidenced by Geraads et al., the determination of the overexpression, which is made by Western blot, comprises the step of lysing the cells and solubilizing the protein to be detected; see entire document (i.e., the preparation of cell extracts), particularly page 1666, column 2.

Furthermore, Von Knebel Doeberitz et al. does not expressly teach whether the cell extracts, which were collected at various times during the course of the determination, were prepared, so as to solubilize the protein, immediately after obtaining the sample or after storage and/or transport in a storage/transportation buffer, but nevertheless the process was necessarily performed one way or the other. According to the description of the Western blot analysis by Geraads et al., cell extracts are prepared immediately after obtaining the sample, but the process involves at least transiently storing and/or transporting the cells in one or another buffer during centrifugation and the subsequent resuspension of the resultant cell pellet before their lysis in lysis buffer; see page 1666, column 2.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

13. Claim 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,709,832 B1, as evidenced by Geraarts et al. (*Am. J. Pathol.* 1999 Jun; **154** (6): 1665-1671), in view of Ryder et al. (*Clin. Chem.* 1988 Dec; **34** (12): 2513-2516).

U.S. Patent No. 6,709,832 B1 (Von Knebel Doeberitz et al.) teaches that which is set forth in the above rejection of claims 1 and 3-6 under 35 U.S.C. 102(e).

However, Von Knebel Doeberitz et al. does not expressly teach the level of cyclin dependent kinase inhibitor p16 is provided as a predetermined value to set up a threshold for the detection procedure.

Ryder et al. teaches predetermining the appropriate cut-off or decision threshold for use in diagnostic applications, which are based upon the measurement of a marker in bodily samples.

It would have been *prima facie* obvious to one ordinarily skilled in the art at the time the invention was made to predetermine the appropriate cut-off or decision threshold for use in practicing the method described by Von Knebel Doeberitz et al. because Ryder et al. teaches predetermining the appropriate cut-off or decision threshold for use in diagnostic applications, which are based upon the measurement of a marker in bodily samples. One ordinarily skilled in the art at the time the invention was made would have been motivated to predetermine the appropriate cut-off or decision threshold for use in practicing the method described by Von Knebel Doeberitz et al. in order to reduce the number of false-positives and/or false-negatives to determine the presence of cervical carcinomas, cervical intraepithelial neoplasias, or cervical carcinomas *in situ* in patients with confidence and accuracy.

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14. Claims 1 and 3-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Khleif et al. (*Proc. Natl. Acad. Sci. USA.* 1996 Apr; **93**: 4350-4354), as evidenced by Bio-Rad Protein Assay² (instruction manual provided with a Bradford assay kit manufactured by Bio-Rad) and the American Type Culture Collection™ (ATCC) catalog³, in view Klaes et al. (*Int. J. Cancer.* 2001; **92**: 276-284) (of record; cited by Applicant).

Khleif et al. teaches a process comprising obtaining a cervical body sample from a human subject (i.e., cervical cancer cells supplied by the American Type Culture Collection, such as HeLa cells), lysing the cells in a lysis buffer, clearing the lysates by centrifugation, and determining the overexpression of the thus solubilized p16^{INK4a} in the prepared samples; see entire document (e.g., the abstract; page 4350, column 2; page 4351, column 1 and Figure 1; and page 4343, column 1).

As evidenced by Bio-Rad Protein Assay, the protein must be solubilized before a determination of the concentration of the protein may be made; see entire document, particularly page 11, item #6.

As evidenced by the ATCC catalog, the cervical cancer cells obtained by Khleif et al., such as HeLa cells, for example, were derived from a sample of an adenocarcinoma of the cervical epithelium of a human subject.

Khleif et al. does not however teach or expressly suggest determining the overexpression of cyclin-dependent kinase inhibitor p16 in a human cervical body sample by comparing the expression level of cyclin-dependent kinase inhibitor p16 within said sample to the expression level present in a healthy human cervical body sample. Furthermore, Khleif et al. does not however teach or expressly suggest acquiring cervical body samples selected from cytological smears, histological specimens, cervical swabs, biopsies, preserved cytological specimens, fixed cell or fixed tissue preparations. In addition, Khleif et al. does not however teach or expressly suggest the level of p16 in the healthy human cervical body sample is determined from a representative number of healthy human cervical samples.

² See http://www.fhcrc.org/science/labs/hahn/methods/biochem_meth/biorad_assay.pdf

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Klaes et al. teaches comparing the body sample to be examined with a corresponding body sample which originates from a healthy person; see entire document (e.g., the abstract; page 277, paragraph bridging columns 1 and 2; page 279, Table 1; page 282, column 2). Klaes et al. teaches acquiring cervical body samples selected from cytological smears, histological specimens, cervical swabs, biopsies, preserved cytological specimens, fixed cell or fixed tissue preparations; see, e.g., page 277, columns 1 and 2. Klaes et al. teaches the level of p16 in the healthy human cervical body sample is determined from a representative number of healthy human cervical samples; see, e.g., page 279, Table 1.

It would have been *prima facie* obvious to one ordinarily skilled in the art at the time the invention was made to practice the method for detecting cervical carcinoma cells according to the method described by Khleif et al. but determining the overexpression of cyclin-dependent kinase inhibitor p16 in a human cervical body sample (i.e., a cervical body sample selected from cytological smears, histological specimens, cervical swabs, biopsies, preserved cytological specimens, fixed cell or fixed tissue preparations) by comparing the expression level of cyclin-dependent kinase inhibitor p16 within the sample acquired from the subject to the expression levels present in representative number of human cervical body samples originating from healthy persons. One ordinarily skilled in the art at the time the invention was made would have been motivated to do so to more accurately determine the overexpression of p16 in the subject, as compared to the level of expression in a the cervical tissue of a healthy unaffected individual.

15. Claim 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over Khleif et al. (*Proc. Natl. Acad. Sci. USA.* 1996 April; **93**:4350-4354) in view of Klaes et al. (*Int. J. Cancer.* 2001; **92**: 276-284) (of record; cited by Applicant), as applied to claims 1 and 3-6 above, and further in view of Ryder et al. (*Clin. Chem.* 1988 Dec; **34** (12): 2513-2516).

³ See <http://www.atcc.com/catalog/numSearch/numResults.cfm?atccNum=CCL-2>.

Klaes et al. and Khleif et al. teach that which is set forth in the above rejection of claims 1 and 3-6 under 35 U.S.C. 103(a).

However, neither Klaes et al. nor Khleif et al. expressly teaches the level of cyclin dependent kinase inhibitor p16 is provided as a predetermined value to set up a threshold for the detection procedure.

Ryder et al. teaches predetermining the appropriate cut-off or decision threshold for use in diagnostic applications, which are based upon the measurement of a marker in bodily samples.

It would have been *prima facie* obvious to one ordinarily skilled in the art at the time the invention was made to predetermine the appropriate cut-off or decision threshold for use in detecting the presence of dysplastic or neoplastic cervical cancer by determining the overexpression of p16 in a cervical sample acquired from a patient because Ryder et al. teaches predetermining the appropriate cut-off or decision threshold for use in diagnostic applications, which are based upon the measurement of a marker in bodily samples. One ordinarily skilled in the art at the time the invention was made would have been motivated to predetermine the appropriate cut-off or decision threshold for use in practicing the method in order to reduce the number of false-positives and/or false-negatives to determine the presence of cervical lesions in patients with confidence and accuracy.

Double Patenting

16. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29

USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

17. Claim 1 and 3-6 rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 4, and 5 of U.S. Patent No. 6,709,832 B1 in view of Khleif et al. (*Proc. Natl. Acad. Sci. USA*. 1996 Apr; **93**: 4350-4354), as evidenced by Bio-Rad Protein Assay⁴ (instruction manual provided with a Bradford assay kit manufactured by Bio-Rad). Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons:

Claims 1, 2, 4, and 5 of U.S. Patent No. 6,709,832 B1 are drawn to a method for detecting cervical carcinomas, cervical intraepithelial neoplasias, or cervical carcinomas *in situ*, said method comprising determining the overexpression of cyclin dependent kinase inhibitor p16 in a human cervical body sample selected from a smear, a organ punctuate, and a biopsy by comparing the expression level of the protein within the sample to the expression level of the protein present in a healthy human cervical body sample. According to claims 5, in particular, the overexpression of p16 is determined by detecting the protein in the sample by a process comprising reacting an antibody directed against the protein with the protein in the sample.

⁴ See http://www.fhcrc.org/science/labs/hahn/methods/biochem_meth/biorad_assay.pdf

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In contrast to claims 1, 2, 4, and 5 of U.S. Patent No. 6,709,832 B1, the instant claims are directed to detecting cervical carcinomas, cervical intraepithelial neoplasias, or cervical carcinomas *in situ* by a process comprising solubilizing the cervical body sample in a lysis buffer and then determining the overexpression of p16 in a human cervical body sample by comparing the expression level of cyclin-dependent kinase inhibitor p16 within said sample to the expression level present in a healthy human cervical body sample.

Khleif et al. teaches a process comprising obtaining a cervical body sample from a human subject (i.e., cervical cancer cells supplied by the American Type Culture Collection, such as HeLa cells), lysing the cells in a lysis buffer, clearing the lysates by centrifugation, and determining the overexpression of the thus solubilized p16^{INK4a} in the prepared samples; see entire document (e.g., the abstract; page 4350, column 2; page 4351, column 1 and Figure 1; and page 4343, column 1).

As evidenced by Bio-Rad Protein Assay, the protein must be solubilized before a determination of the concentration of the protein may be made; see entire document, particularly page 11, item #6.

Accordingly, it would have been *prima facie* obvious to one ordinarily skilled in the art at the time of the invention to have practiced the method according to claims 1, 2, 4, and 5 of U.S. Patent No. 6,709,832 B1 by solubilizing the cervical body sample in a lysis buffer before determining the overexpression of p16 in a human cervical body sample by comparing the expression level of cyclin-dependent kinase inhibitor p16 within said sample to the expression level present in a healthy human cervical body sample.

18. Claim 2 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over U.S. Patent No. 6,709,832 B1 in view of Khleif et al. (*Proc. Natl. Acad. Sci. USA*. 1996 Apr; **93**: 4350-4354), as evidenced by Bio-Rad Protein Assay⁵ (instruction manual provided with a Bradford assay kit manufactured by

⁵ See http://www.fhcrc.org/science/labs/hahn/methods/biochem_meth/biorad_assay.pdf

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Bio-Rad), as applied to claims 1, 2, 4, and 5 above, in further view of Ryder et al. (*Clin. Chem.* 1988 Dec; **34** (12): 2513-2516). Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons:

Neither claims 1, 2, 4, and 5 of U.S. Patent No. 6,709,832 B1 nor Khleif et al. expressly teaches or suggests the level of cyclin dependent kinase inhibitor p16 is provided as a predetermined value to set up a threshold for the detection procedure.

Ryder et al. teaches predetermining the appropriate cut-off or decision threshold for use in diagnostic applications, which are based upon the measurement of a marker in bodily samples.

It would have been *prima facie* obvious to one ordinarily skilled in the art at the time the invention was made to predetermine the appropriate cut-off or decision threshold for use in practicing the method of claims 1, 2, 4, and 5 of U.S. Patent No. 6,709,832 B1 using methodology described by Khleif et al. because Ryder et al. teaches predetermining the appropriate cut-off or decision threshold for use in diagnostic applications, which are based upon the measurement of a marker in bodily samples. One ordinarily skilled in the art at the time the invention was made would have been motivated to predetermine the appropriate cut-off or decision threshold for use in practicing the method of claims 1, 2, 4, and 5 of U.S. Patent No. 6,709,832 B1 using methodology described by Khleif et al. in order to reduce the number of false-positives and/or false-negatives to determine the presence of cervical carcinomas, cervical intraepithelial neoplasias, or cervical carcinomas *in situ* in patients with confidence and accuracy.

19. Claims 1 and 3-6 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-26, 33, 34, and 36-40 of copending Application No. 10/633,484 in view of Klaes et al. (*Int. J. Cancer.* 2001; **92**: 276-284) (of record; cited by Applicant). Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons:

Claims 1-26, 33, 34, 36-38 of copending Application No. 10/633,484 are drawn to a method for diagnosing a medically relevant condition of patient, namely a cancer of

the reproductive system, or more particularly cervical dysplasia, cervical cancer and their respective precursor stages by a process comprising preparing a solution containing the protein present in a cervical sample (i.e., a swab, a cell, a tissue, a biopsy), detecting the level of cyclin dependent kinase inhibitor p16 in the solubilized sample of proteins, and normalizing the detected level with respect to at least one normalization parameter or marker.

In contrast to claims 1-26, 33, 34, and 36-40 of copending Application No. 10/633,484, the instant claims are directed to detecting cervical carcinomas, cervical intraepithelial neoplasias, or cervical carcinomas *in situ* by a process comprising determining the overexpression of p16 in a human cervical body sample by comparing the expression level of cyclin-dependent kinase inhibitor p16 within said sample to the expression level present in a healthy human cervical body sample, albeit without first normalizing the levels of the protein with respect to at least one normalization parameter or marker.

Klaes et al. teaches comparing the body sample to be examined with a corresponding body sample which originates from a healthy person; see entire document (e.g., the abstract; page 277, paragraph bridging columns 1 and 2; page 279, Table 1; page 282, column 2). Klaes et al. teaches the level of p16 in the healthy human cervical body sample is determined from a representative number of healthy human cervical samples; see, e.g., page 279, Table 1.

It would have been *prima facie* obvious to one ordinarily skilled in the art at the time the invention was made to practicing the method of claims 1-26, 33, 34, and 36-40 of copending Application No. 10/633,484 by determining the overexpression of cyclin-dependent kinase inhibitor p16 in a human cervical body sample (i.e., a cervical body sample selected from cytological smears, histological specimens, cervical swabs, biopsies, preserved cytological specimens, fixed cell or fixed tissue preparations) by comparing the normalized expression level of cyclin-dependent kinase inhibitor p16 within the sample acquired from the subject to the normalized expression levels present in representative number of human cervical body samples originating from healthy persons. One ordinarily skilled in the art at the time the invention was made would have

been motivated to do so to more accurately determine the overexpression of p16 in the subject, as compared to the level of expression in a the cervical tissue of a healthy unaffected individual.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

20. Claims 1 and 3-6 are directed to an invention not patentably distinct from claims 1-26, 33, 34, and 36-40 of commonly assigned copending Application No. 10/633,484. Specifically, although the conflicting claims are not identical, they are not patentably distinct from each other for the reasons set forth above in the provisionally rejection of the claims on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-26, 33, 34, and 36-40 of copending Application No. 10/633,484 in view of Klaes et al. (*Int. J. Cancer.* 2001; 92: 276-284) (of record; cited by Applicant).

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302). Commonly assigned copending Application No. 10/633,484, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 35 U.S.C. 103(c) and 37 CFR 1.78(c) to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications filed on or after November 29, 1999.

21. Claims 1-6 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10, 14-16, 42-50, 52-57, and 85 of copending Application No. 10/569,758. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons:

The claimed inventions are so substantially similar that for the most part, the claimed subject matter of the copending application anticipates the claimed subject matter of the instant application and any minor differences in the subject matter claimed in the instant application would be seen as an obvious variation of the subject matter claimed in the copending application.

22. Claims 1-6 are directed to an invention not patentably distinct from claims 1-10, 14-16, 42-50, 52-57, and 85 of commonly assigned copending Application No. 10/569,758. Specifically, although the conflicting claims are not identical, they are not patentably distinct from each other for the reasons set forth above in the provisionally rejection of the claims on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10, 14-16, 42-50, 52-57, and 85 of copending Application No. 10/569,758.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302). Commonly assigned copending Application No. 10/569,758, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 35 U.S.C. 103(c) and 37 CFR 1.78(c) to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications filed on or after November 29, 1999.

Conclusion

23. No claim is allowed.
24. The prior art made of record and not relied upon is considered pertinent to Applicant's disclosure. Sano et al. (*Pathology International*. 1998; **48**: 580-585) teaches immunohistochemical overexpression of p16 in cervical cancer and cervical intraepithelial neoplasia.
25. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1643

slr
August 7, 2006